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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/623,138	08/28/2000	Shigeru Kinoshita	KINOSHITA3	9673

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EXAMINER

HUI, SAN MING R

ART UNIT PAPER NUMBER

1617

DATE MAILED: 07/30/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

09/623,138

Applicant(s)

KINOSHITA, SHIGERU

Examiner

San-ming Hui

Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on March 25, 2002, May 16, 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 11,14,15,17,19 and 20 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 11,14,15,17,19 and 20 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                             | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____  |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)         | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____                                    |

### **DETAILED ACTION**

The cancellation of claims 1-10, 12, 13, 16, and 18 in amendment filed March 25, 2002 is acknowledged. The amendment of claims 11, 14, 17, 19, and 20 in amendments filed March 25, 2002 and May 16, 2002 have been entered.

Claims 11, 14-15, 17, and 19-20 are pending. The pending claims are now drawn to a method of inhibiting Langerhans cells migration.

The outstanding rejections under 35 USC 112, first paragraph and 35 USC 102 are withdrawn in view of the amendments filed March 25, 2002 and May 16, 2002.

### ***Claim Objections***

Claim 14 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 14 recites "22-oxacalcitriol" which is not a limitation recited in the independent claim 11.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17, 19 and 20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as

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to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In the instant case, the limitations "Langerhans cells causes keratoconjunctivitis" in claim 17, "Langerhans cells causes phlyctenular keratitis or corneal infiltration" in claim 19 and "production of interleukin-1 in corneal epithelial cells caused by Langerhans cell migration" in claim 20 are not found to be supported by the originally filed claims and specification.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 11, 14-15, 17, and 19-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dam et al. (Journal of Investigational Dermatology Symposium proceedings; 1996;1(1):72-77) in view of Itoh et al. (WO96/29079, the English translation, Patent US 6,248,732, is also provided), Hingorani et al. (Drugs 1995; 50(2); 208-221), and Muller et al. (Journal of Investigational Dermatology Symposium proceedings; 1996;1(1): 68-71).

Dam et al. teaches calcitriol and calcipotriol are useful to suppress the number of Langerhans cells (LC) when applied topically (See particularly page 72, col. 2, last paragraph). Dam et al. also teaches calcitriol or calcipotriol inhibit THF- $\alpha$ , a factor which can induce migration of LC (See page 76, col. 1, 2nd paragraph). Dam et al. also

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teaches calcitriol and calcipotriol suppress the T-cell proliferation (See page 75, col. 2, first paragraph).

Dam et al. does not teach calcitriol is in a form of ophthalmic solution. Dam et al. does not expressly teach calcitriol is useful in treating keratoconjunctivitis and preventing phlyctenular keratitis or corneal infiltration. Dam et al. does not expressly teach calcitriol is useful in a method to inhibit interleukin-1 production in cornea epithelium.

Itoh et al. teaches that calcitriol can be formulated into an ophthalmic composition (See See particularly col. 11, line 5-10).

Hingorani et al. teaches atopic keratoconjunctivitis is a T-cell inflammation prominent disorder (See particularly abstract). Hingorani et al. also teaches atopic keratoconjunctivitis may lead to infiltration and corneal involvement such as epithelial keratitis (See particularly page 210, col. 1, last paragraph).

Muller et al. teaches the calcitriol inhibits the production of interleukin-1 at a presecretory level such as reducing the levels of interleukin-1 $\alpha$  mRNA (See page 68, col.2, third paragraph).

It would have been obvious to one skill in the art when the invention was made to employ calcitriol, in ophthalmic solution dosage form, in a method to treat keratoconjunctivitis and prevent phlyctenular keratitis or corneal infiltration. It would have been obvious to one skill in the art when the invention was made to employ calcitriol in a method to inhibit interleukin-1 production in cornea epithelium, thus precisely, the obvious therapeutic benefit herein recited.

One of ordinary skill in the art would have motivated to employ calcitriol, in ophthalmic solution dosage form, in a method to treat keratoconjunctivitis and prevent phlyctenular keratitis or corneal infiltration because it is known that atopic keratoconjunctivitis is a T-cell inflammation prominent disorder and may lead to infiltration and corneal involvement such as epithelial keratitis. Therefore, employing any T-cell proliferation inhibitor, including calcitriol would have been reasonably expected to treat keratoconjunctivitis and prevent keratitis, including phlyctenular keratitis or corneal infiltration, thereby. Furthermore, One of ordinary skill in the art would have motivated to employ calcitriol in a method to inhibit interleukin-1 production in cornea epithelium because calcitriol is known to inhibit the production of interleukin-1 $\alpha$  at a presecretory level by reducing the level of interleukin-1 $\alpha$  mRNA. One of ordinary skill in the art would therefore reasonably expect calcitriol be useful in inhibiting the production of interleukin-1 regardless of whether the interleukin-1 is secreted by corneal epithelium or not.

It is applicant's burden to demonstrate unexpected results over the prior art. See MPEP 716.02, also 716.02 (a) - (g). Furthermore, the unexpected results should be demonstrated with evidence that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance. *Ex parte Gelles*, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992). Moreover, evidence as to any unexpected benefits must be "clear and convincing" *In re Lohr*, 137 USPQ 548 (CCPA 1963), and be of a scope reasonably commensurate with the scope of the subject matter claimed, *In re Linder*, 173 USPQ 356 (CCPA 1972). In the instant case, the examples in the

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instant specification have been considered, but are not found persuasive. the instant example merely demonstrates that calcitriol is efficient in inhibiting the migration of LC based on the decreased number of LC present in corneal epithelium. This is seen to be an expected effect based on the cited prior art. No convincing and clear unexpected result is seen.

### ***Response to Arguments***

Applicant's arguments filed March 25, 2002 averring that it has been unknown that monocytes are present in eyes in such amount have been fully considered but they are not persuasive. There is no evidence presented to teach away from obvious use herein reciting, thus, the presented arguments fail to rebut the obviousness rejection set forth in the office action. Absent evidence to the contrary, one of ordinary skill in the art would employ calcitriol in a method of inhibiting LC migration. Please note that it is the applicant's burden to illustrate with evidence that the cited prior art would not render obvious.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within

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TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (703) 305-1002. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Minna Moezie, J.D., can be reached on (703) 308-4612. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

San-ming Hui  
July 26, 2002

  
RUSSELL TRAVERS  
PRIMARY EXAMINER  
GROUP 1200